Remarks

Reconsideration of this Application is respectfully requested.

Upon entry of the foregoing amendment, claims 2-4, 7-29, 44-47, and 51-52 are pending in the application, with claim 2 being the independent claim. Claims 1, 5-6, and 48-50 have been cancelled herein without prejudice to or disclaimer of the subject matter therein. Applicants reserve the right to pursue the subject matter of the cancelled claims in a continuing application. Claims 2, 12-18, 24, 26, and 44 have been amended, and claims 51-52 have been added. The amendments place the application in condition for allowance or remove issues for appeal and do not require further search. Entry is respectfully requested.

New claims 51-52 read on the elected species. Upon allowance of generic claim 2, Applicants respectfully request consideration of the withdrawn claims that recite non-elected species. 37 C.F.R. § 1.141; *see also* Restriction Requirement mailed July 12, 2002, p. 6, lines 13-17.

Support for the amendment of the claims may be found in the specification, for example, at page 23, paragraph [0065]; page 24, paragraph [0066]; page 25, paragraph [0070], page 27, paragraph [0073]; and page 34, paragraph [0091]. Support for the new claims may be found, for example, in original claim 2.

It is believed these changes introduce no new matter. Their entry is respectfully requested.

Based on the above amendment and the following remarks, Applicants respectfully request that the Examiner reconsider all outstanding objections and rejections and request that they be withdrawn.

Rejection Under 35 U.S.C. § 112 - New Matter

Claims 1-3, 7, 10-18, 24, 26-28, and 44-50 were rejected under 35 U.S.C. § 112, first paragraph, as allegedly containing new matter in the recitation of "not in the RNase H domain" and "with the proviso that said reverse transcriptase is not a Murine Moloney Leukemia Virus (M-MLV) reverse transcriptase with a methionine mutation at amino acid position valine 223."

Although Applicants respectfully disagree with the rejection, Applicants have cancelled claims 1 and 49. The pending claims do not recite the language that the Examiner found objectionable. The rejection is therefore moot.

Rejection Under 35 U.S.C. § 112 - Written Description

Claims 1-3, 7, 10-18, 24, 26-28, and 44-50 were rejected under 35 U.S.C. § 112, first paragraph, as allegedly containing subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the art that the inventors had possession of the claimed invention. The Office Action states that there are no common attributes, no structural limitations, and no disclosure of requirements that provide guidance on which sequences meet the functional limitations of enhanced thermostability. Applicants respectfully traverse this rejection.

The Office Action states that "the claims fail to meet the written description requirement by encompassing sequences which are not described in the specification." (Office Action, p. 7, lines 1-2; *see also* p. 4, lines 4-5). Applicants respectfully disagree.

The written description requirement certainly does *not* require a description of every species within a claimed genus, contrary to the statements on pages 4 and 7 of the Office

Action. MPEP 2163, p. 2100-169, col. 1 (Rev. 1, Feb. 2003). The courts and the PTO have stated that a specification need only describe a representative number of species sufficient to show that the inventors were in possession of the genus recited in the claims. *Eli Lilly,* 119 F.3d at 1568, 43 USPQ2d at 1406 (Fed. Cir. 1997). Further, the number of species needed to be a "representative" number is inverse to the skill and knowledge in the art. MPEP 2163, p. 2100-169, col. 1. Additionally, a description of a genus may be adequate even though it fails to describe any particular species. MPEP 2163, p. 2100-169, cols. 1-2.

Moreover, the Federal Circuit has recently emphasized that functional descriptions of genetic material may be adequate to meet the written description requirement if, in the art, that function is correlated with a known structure. *Moba, B.V. v. Diamond Automation, Inc.*, Nos. 01-1063 and 01-1083, 2003 U.S. App. Lexis 6285, at *31-32 (Fed. Cir., Apr. 1, 2003)[1]; *see also*, *Amgen Inc. v. Hoechst Marion Roussel Inc.,* 314 F.3d. 1313, 1332 (Fed. Cir. 2003) (citing *Enzo Biochem, Inc. v. Gen-Probe Inc.*, 63 U.S.P.Q.2d, 1609 (Fed. Cir. 2002)).

Additionally, the description only needs to describe what is new or not conventional. *See Hybritech Inc. v. Monoclonal Antibodies, Inc.,* 802 F.2d at 1384, 231 USPQ at 94; MPEP 2163, p. 2100-165, col. 2 (Rev. 1, Feb. 2003).

Applicants also note that there are no outstanding enablement rejections in the application. The Federal Circuit recently stated that

> In Enzo and Amgen, the record showed that the specification that taught one of ordinary skill in the art to make and use an invention also convinced that artisan that the inventor possessed the invention.

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[1] A copy is attached herewith for the convenience of the Examiner.

Moba, B.V. v. Diamond Automation, Inc., 2003 U.S. App. Lexis 6285, at *32-33. Therefore, the finding by the PTO that the claims are enabled is further evidence that one of ordinary skill in the art would have recognized that Applicants had possession of the claimed invention.

1. Breadth of the Claims

Applicants note that the pending claims are directed to a "retroviral" reverse transcriptase having "RNA-dependent DNA polymerase activity." Retroviral reverse transcriptases having the recited activity have a conserved structure, as discussed in detail below. Thus, the claimed genus does not encompass proteins having *any* sequence, contrary to the statements in the Office Action.

2. The Present Facts Are Distinguishable From Eli Lilly

The Office Action cited *The Regents of University of California v. Eli Lilly and Co.*, 43 USPQ2d 1398 (Fed. Cir. 1997) to support this rejection. However, the facts in *Eli Lilly* differ significantly from the present facts.

In *Eli Lilly*, the claims were directed to "vertebrate" and "mammalian" cDNA encoding insulin. The specification reduced to practice and described only rat insulin cDNA. No other insulin cDNAs were known, disclosed, or reduced to practice.

In contrast, in the present application, the specification describes a number of different, known wild-type reverse transcriptases, mutant reverse transcriptases, and functional regions and consensus sequences of reverse transcriptases, as discussed in the Amendment and Reply filed January 16, 2003 and below. Additional wild-type reverse transcriptases, mutants, functional regions, and consensus sequences were known in the art prior to the priority application filing date, as discussed below. Importantly, the specification

also describes numerous novel mutations that enhance or decrease particular activities of reverse transcriptases (e.g., thermostability, TdT activity, fidelity, etc.). Applicants assert that in view of the species described in the present specification and the well developed state of the reverse transcriptase art, the present situation is different from the situation in *Eli Lilly*.

3. The Present Facts Are Analogous To Example 16 In The PTO Synopsis

The hypothetical claim in Example 16 of the PTO's *Synopsis of Application of Written Description Guidelines* ("*The PTO Synopsis*") is directed to an "isolated antibody capable of binding to antigen X." *The PTO Synopsis*, p. 59. The example also states that the specification contains an example in which antibodies against antigen X were "contemplated," but not reduced to practice. *Id.*

Although neither the hypothetical claim nor the specification in Example 16 recite any explicit structure for the claimed antibody, *The PTO Synopsis* nevertheless concludes that the specification meets the written description requirements. *Id.*, p. 60. The reasons given are the following: (1) the functional features of antibody binding, (2) methods for making antibodies were routine in the art, (3) antibody technology was well developed (e.g., the sequences of constant and variable regions of antibodies from a variety of species were published), and (4) the five classes of antibody have well defined structural characteristics (i.e., a constant region, and a variable region containing complementarity determining regions and framework regions, which form the antigen binding sites). *Id.*, pp. 59 and 60.

Like Example 16, in the present situation, (1) the claims recite a functional characteristic, (2) methods of producing, modifying and mutating reverse transcriptases were routine, (3) the reverse transcriptase art was well developed, as discussed below, and (4)

retroviral reverse transcriptases have well defined structural characteristics, also as discussed below.

4. The Reverse Transcriptase Art Is Well Developed and Reverse Transcriptases Have Well Defined Structural Characteristics

The sequences for numerous wild-type reverse transcriptases were known. For example, the nucleotide sequences for M-MLV reverse transcriptase, AMV reverse transcriptase, RSV reverse transcriptase, and HIV reverse transcriptase were known, some more than 20 years ago. *See* specification, p. 41, paragraph [0114] (listing Shinnick *et al.*, *Nature 293*:543-548 (1981) (IDS Document AT12); Joliot *et al.*, *Virology 195*:812-819 (1993); Schwartz, *et al.*, *Cell 32*:853-859 (1983); Ratner *et al.* (cited as "Wong-Staal *et al.*" in the specification), *Nature 313*:277-284 (1985)).[2,3] Sequences of wild-type reverse transcriptase sequences from other retroviruses were also known. Applicants will provide citations for publications disclosing such sequences upon request.

In addition to the sequences of wild-type reverse transcriptases, the sequences of many mutant reverse transcriptases were also known. For example, reverse transcriptases having reduced or substantially reduced RNase H activity have been previously described. *See, e.g.,* specification, p. 34, paragraph [0092] (listing U.S. Patent 5,668,005 (IDS Document AE1), U.S. Patent 6,063,608 (IDS Document AF1), and PCT Publication No. WO 98/47912 (IDS Document AI1)). Other IDS documents for the present application also disclose the sequences of mutant reverse transcriptases. Applicants will provide citations

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[2] Copies attached herewith for the convenience of the Examiner.

[3] Applicants note that all publications cited in the application are fully incorporated by reference in the present application. *See* paragraph [0191] on page 76.

upon request. Therefore, by analogy to Example 16 of *The PTO Synopsis*, the numerous published reverse transcriptase sequences show that the reverse transcriptase art was well developed.

Further, a great deal is known about the structure of reverse transcriptases. For example, Johnson *et al.* published an alignment of RSV, M-MLV, HIV and other reverse transcriptase sequences in 1986, which showed that reverse transcriptases have significant conservation between a 150-residue segment in their carboxyl termini (the RNase H domain) and a 250 residue segment in their amino termini (the polymerase domain). Johnson, M.S. *et al. PNAS USA 83*:7648-7652 (1986), p. 7649-50, figures 2-4.[4] Johnson *et al.* pointed out residues that are conserved between the sequences and identified consensus sequences and motifs. *Id.* One of the motifs Johnson *et al.* identified was the polymerase consensus motif corresponding to positions 337 to 353 of M-MLV reverse transcriptase. The authors also identified positions, for example, those corresponding to residues 210, 216, 218, 224, 231, 235, 237, 240, 271, 274, 277, 290, 291, 309-312, and 316-317, as being identical across the aligned sequences.

Additionally, the tertiary structure of reverse transcriptases was known. For example reverse transcriptases contain a hand domain comprised of fingers, palm, thumb and connection subdomains. *See, e.g.,* Kohlstaedt, L.A. *et al.*, *Science 256*:1783-1790 (1992) (IDS Document AS7) and Georgiadis, M.M., *et al.*, *Structure 3*:879-892 (1995) (IDS Document AT4). The specification describes this domain at page 29, paragraph [0079]. Moreover, Georgiadis *et al.* determined the crystal structure of a proteolytic fragment of M-MLV reverse transcriptase, and compared it to the published crystal structure of HIV reverse

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[4] Copy attached herewith for the convenience of the Examiner.

transcriptase. They found that the overall fold and structures of the fingers and palm domains in M-MLV and HIV-1 reverse transcriptase are very similar. Georgiadis *et al.*, p. 883, col. 1.

Georgiadis *et al.* found that the fingers domain of M-MLV reverse transcriptase is composed of a highly twisted five-stranded mixed sheet, three α helices, and two β hairpin structures, one of which is part of the sheet. Georgiadis *et al.*, p. 880, col. 2. The palm domain of M-MLV reverse transcriptase is composed of a four-stranded antiparallel β sheet and two long α helices in the core of the domain, a β hairpin in the primer grip region, two short α helices, a short 3_{10} helix, and another short α helix. *Id.*, p. 881, col. 1. The fingers and palm domains also contain conserved resides including Lys53, Gln63, Ser195, and Gln260 of M-MLV reverse transcriptase. *Id.*, p. 881, col. 2.

At the junction of the fingers and palm domains lies the polymerase active site. *Id.*, p. 884, col. 1. This site contains three Asp residues (at positions 150, 224 and 225 of M-MLV reverse transcriptase) that are required for polymerase activity. *Id.* The polymerase site in M-MLV reverse transcriptase contains a type II' turn. *Id.*, p. 885, col. 2. HIV-1 reverse transcriptase also contains a type II' turn at the equivalent site. *Id.* In other proteins, position 2 of type II' turns is commonly a Gly residue but in all known wild-type reverse transcriptases, there is a non-Gly residue at this position. *Id.* The residues and interactions that stabilize this structure were also identified. *Id.*, p. 885, col. 2 to p. 886, col. 1.

Georgiadis *et al.* also used the crystal structure of M-MLV and the conserved residues across murine, avian and human reverse transcriptases to identify the structures involved in fidelity, processivity, and selectivity for dNTPs. For example, Georgiadis *et al.* state:

> the highly conserved residues Gln190 (151 in HIV-1 RT) and Gly191 (152 in HIV-1 RT) found in the conserved sequence LPQG within loop β_9-α_H (part of motif B, a conserved sequence found on RTs []), form hydrogen bonds in the minor groove to O2 or N3 of the dNTP and template base, respectively.

Id., p. 886. col. 2. They also state that conserved residues Lys103, Arg 110, and Asp114 interact with the template strand, and Arg116 and Asn119 interact with the primer strand. *Id.*, p. 887, col. 2. With regard to selectivity for dNTPs, Georgiadis *et al.* state that the interaction between Phe155 and the 2'-hydroxyl of a ribose nucleotide disfavors rNTP, and that Tyr - the only other residue found at that position in reverse transcriptases - would result in the same selectivity as Phe. *Id.*, p. 888, col. 1. Based on the results of Georgiadis *et al.*, Gao *et al.* mutated Phe155 and determined that a substitution with valine allows reverse transcriptase to incorporate rNTPs. Gao, G. *et al.*, *Proc. Natl. Acad. Sci. USA 94*:407-411 (1997).[5] Clearly, as the evidence above shows, the structure of reverse transcriptases is well defined and highly conserved.

5. Summary

As detailed above, Applicants submit that the reverse transcriptase art is well developed and reverse transcriptases have a well defined structure. Thus, the present situation is analogous to the situation for immunoglobulins in Example 16 of *The PTO Synopsis*. Additionally, there is a correlation between the recited "RNA-dependent DNA polymerase activity" and a known structure, e.g., the hand domain discussed above.

Applicants therefore respectfully submit that based on the present specification, one of ordinary skill in the art would readily recognize that Applicants, at the time the present

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[5] Copy attached herewith for the convenience of the Examiner.

application was filed, had possession of the claimed invention. Accordingly, reconsideration and withdrawal of this rejection are respectfully requested.

Rejection Under 35 U.S.C. § 102 - Blain et al.

The Office Action, at page 7, maintained the rejection of claims 1, 16-18, 24, and 26-28 under 35 U.S.C. § 102(b) as allegedly being anticipated by Blain *et al.* (*J. Biol. Chem.* *268*:23585-2392 (1993), PTO-892 document U). Applicants respectfully traverse this rejection.

Claim 1 has been cancelled, and claims 16-18, 24, and 26-28 have been amended to depend ultimately from claim 2. Therefore, the rejection is moot.

Rejection Under 35 U.S.C. § 102 - Arakawa et al.

The Office Action, at page 8, maintained the rejection of claims 1, 12-18, 24, and 26-28 under 35 U.S.C. § 102(a) as allegedly being anticipated by Arakawa *et al.* (Japanese patent application 2000-139457, PTO-892 document N). Applicants respectfully traverse this rejection.

Claim 1 has been cancelled, and claims 12-18, 24, and 26-28 have been amended to depend ultimately from claim 2. Therefore, the rejection is moot.

Rejection Under 35 U.S.C. § 103

The Office Action, at page 9, maintained the rejection of claims 44-47 under 35 U.S.C. § 103(a) as allegedly being unpatentable over Blain *et al.*, cited *supra*, or Arakawa *et*

al., cited *supra*, in view of Stratagene Catalog, page 39 (1988). Applicants respectfully traverse this rejection.

Claims 44-47 have been amended to depend ultimately from claim 2. Therefore, the rejection is moot.

Information Disclosure Statement

Contrary to the statement in the Office Action, the Information Disclosure Statements filed November 2, 2001 and June 25, 2002 did include copies of the cited documents, as evidenced by the enclosed date-stamped post card receipts (copies of the post-card receipts were also submitted with the Amendment and Reply filed on January 16, 2003). However, Applicants herewith submit copies of the relevant references for the Examiner's convenience. It is respectfully requested that the Examiner initial and return a copy of the forms PTO-1449 filed on November 2, 2001 and June 25, 2002, and indicate in the official file wrapper of this patent application that these cited documents have been considered.

Conclusion

All of the stated grounds of objection and rejection have been properly traversed, accommodated, or rendered moot. Applicants therefore respectfully request that the Examiner reconsider all presently outstanding objections and rejections and request that they be withdrawn. Applicants believe that a full and complete reply has been made to the outstanding Office Action and, as such, the present application is in condition for allowance. If the Examiner believes, for any reason, that personal communication will expedite

prosecution of this application, the Examiner is invited to telephone the undersigned at the number provided.

Prompt and favorable consideration of this Amendment and Reply is respectfully requested.

Respectfully submitted,

STERNE, KESSLER, GOLDSTEIN & FOX P.L.L.C.

Helene C. Carlson
Agent for Applicants
Registration No. 47,473

Date: July 7, 2003
1100 New York Avenue, N.W.
Washington, D.C. 20005-3934
(202) 371-2600

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